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## ***SUPPORTING INFORMATION***

***Title:*** A One-Pot Asymmetric Sequential Amination-Alkylation of Aldehydes: Expedient Synthesis of Aliphatic Chiral Amines

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***Ref. No.:*** O200600781

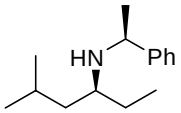
**General Experimental Details:** NMR spectra were recorded on JEOL ECX 400 spectrometer, operating at 400 MHz ($^{1}$H) and 100 MHz ($^{13}$C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS (= 0) or relative to $CHCl_3$ (7.26 ppm) for $^{1}$H NMR. For $^{13}$C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad. The coupling constants are expressed in Hz. FTIR spectra were obtained on Nicolet Avatar 370 spectrometer. Mass spectra were recorded on a Finnigan MAT 95 (EI) with an ionization potential of 70 eV. Elemental analyses were performed at Analytische Laboiratorien, Lindlar, Germany on an Elementar Vario EL III instrument. For amine products **2**, reaction progress and diastereomeric excess measurements were obtained using a Shimadzu GC-2010 instrument with a Rtx-5 amine column (Restec, 30 m x 0.25 mm); $T_{inj}$ = 300 °C and $T_{det}$ = 300 °C were always constant; Program A: 50 °C (0 min), then 20 °C/min to 145 °C (hold 40 min), then 40 °C/min to 280 °C (hold 2 min); Program B: 50 °C (1 min), then 30 °C/min to 130 °C (hold 1 min), then 3 °C/min to 170 °C (hold 0 min), then 30 °C/min to 280 °C (hold 2 min); Program C: 50 °C (0 min), then 20 °C/min to 170 °C (hold 9 min), then 20 °C/min to 280 °C (hold 2 min); Program D: 50 °C (0 min), then 14 °C/min to 280 °C (hold 2 min); Program E: 50 °C (0 min), then 14 °C/min to 160 °C (hold 5 min), then 20 °C/min to 280 °C (hold 2 min); Program F: 50 °C (0 min), then 30 °C/min to 160 °C (hold 50 min), then 40 °C/min to 280 °C (hold 2 min); Program G: 50 °C (0 min), then 20 °C/min to 190 °C (hold 7 min), then 20 °C/min to 280 °C (hold 2 min) and Program H: 50 °C (1 min), then 14 °C/min to 130 °C (hold 5 min), then 2 °C/min to 170 °C (hold 0 min), then 30 °C/min to 280 °C (hold 2 min). For hydrogenolyzed products (primary amines **3**) the enantiomeric excesses of the trifluoroacetamide derivative was determined by gas chromatography using a Shimadzu GC-2010 instrument on a Chiraldex B-DP column (Astec, 30 m x 0.25mm); $T_{inj}$ = 200 °C, $T_{det}$ = 200 °C and carrier gas He @ 23.6 psi were constant; Program I: 120 °C (15 min), then 15 °C/min to 180 °C (hold 10 min) split ratio 60:1; Program J: 85 °C (80 min), the 15 °C/min to 180 °C (hold 10 min), split ratio 60:1 and Program K: 95 °C isothermal, split ratio 60:1. Column chromatography was performed using silica gel 60 (0.040-0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 $F_{254}$ and visualized under ultraviolet irradiation (254 nm).

All reactions were performed under an inert atmosphere (argon or nitrogen). Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled from sodium benzophenone ketyl. All reagents were obtained from Sigma-Aldrich and used without further purification except the following: heptaldehyde was distilled from $CaCl_2$. Copper(I) iodide (99.999% purity, Aldrich catalog number, 215554); copper(I) bromide (99.999% purity, Aldrich catalog number, 254185); copper(I) cyanide (99.98% purity, Aldrich catalog number, 455911); butyllithium solution (2.5 M in hexanes, Sigma-

Aldrich catalog number, 230707); butylmagnesium chloride solution (2.0 M in tetrahydrofuran, Aldrich catalog number, 291005); ethylmagnesium chloride solution (2.0 M in tetrahydrofuran, Aldrich catalog number, 303828); methylmagnesium chloride solution (3.0 M in tetrahydrofuran, Aldrich catalog number, 189901); boron trifluoride diethyl etherate (Fluka catalog number, 15719); $Ti(O\textit{i}Pr)_4$ (99.999% grade, Aldrich catalog number, 377996). The (*S*)-α-methylbenzylamine (Aldrich catalog number, 115568) was of 98% chemical purity and 98% *ee*. $Pd(OH)_2/C$ (≤ 50% water, 20 wt % loading (dry basis)) was purchased from Aldrich (catalog number, 212911). Pd/C (≤ 50% water, 5 wt % loading (dry basis)) was purchased from Aldrich (catalog number, 276707).

**General procedure for the synthesis of (2) using CuBr with THF or $Et_2O$ as a solvent:** A round-bottom flask containing anhydrous CuBr (2.0-6.0 equiv) was gently heated (< 80 °C) by heat gun under high vacuum for 5 min, flushed with nitrogen, cooled to room temperature, and then THF or $Et_2O$ (30.0-35.0 mL, in total 39.0-44.0 mL, 0.10-0.08 M) was added. This solution was cooled to -45 °C and RMgCl in THF (4.0-12.0 equiv) was added over five min. This solution was then further stirred at -45 °C for 15 min, and then cooled to -78 °C. $BF_3{\cdot}OEt_2$ (2.0-6.0 equiv) was added over two min, and the solution was stirred for 5 min. A prestirred (0.5 h at room temp.) solution of the aldehyde (5.0 mmol, 1.0 equiv), THF or $Et_2O$ (7.0 mL), $Ti(O\textit{i}Pr)_4$ (73 μL, 0.25 mmol, 0.05 equiv) and (*S*)-α-MBA (0.68 mL, 5.25 mmol, 1.05 equiv) was then added via cannula over 20-25 min. Additional THF or $Et_2O$ (2.0 mL) was added to the residual imine and the resulting solution was added via cannula to the reaction flask. The reaction solution was then stirred at -78 °C for 2 h, then at -45 °C for 1 h. The reaction was then quenched by the addition of a mixture of saturated $NH_4Cl$ and 25% $NH_4OH$ (7:3 ratio, 30 mL in total) at -45 °C and was stirred for 5 min. The cooling bath was removed and stirring continued for another 90 min at room temp. $Et_2O$ (20 mL) was added, and the biphasic solution was stirred for 5 min. The reaction mixture was then filtered through a bed of celite and the celite subsequently washed with $Et_2O$ (3 × 25 mL). The aqueous phase was extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were washed with saturated $NH_4Cl$ (2 × 25 mL), then with brine (2 × 20 mL), dried over $Na_2SO_4$, filtered, and then evaporated to dryness to obtain the crude product (the *de* was measured with unpurified material). Purification by silica gel flash chromatography to provide the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (note that amine products are considered semi-volatile and converted in to HCl salt, then kept under high vacuum (defined as 0.5 mm Hg) for ≥ 24 h.). The major (*S*,*S*) diastereomer was isolated in pure form either after further flash chromatography or by the recrystallization of the HBr or HCl salt.

**(3S)-5-methyl-*N*-((S)-1-phenylethyl)hexan-3-amine (2b):**



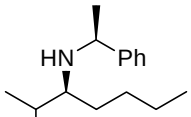

**2b**

**CuBr with THF as a solvent:** Reaction details: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv), CuBr (2.87 g, 20.0 mmol, 4.0 equiv), EtMgCl in THF (20.0 mL, 2.0 M, 40.0 mmol, 8.0 equiv), $BF_3{\cdot}OEt_2$ (2.54 mL, 20.0 mmol, 4.0 equiv), THF (39.0 mL, 0.08 M); 83% *de*. Purification by silica gel flash chromatography (heptanes/EtOAc/$NH_4OH$, 93:5:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.08 g, 84% yield). The major (*S*,*S*) diastereomer was isolated in pure form by the recrystallization (heptanes:EtOH) of the HCl salt. GC (program B, see General Experimental Details): retention time [min]: major (*S*,*S)*-2b isomer, 15.2; minor (*R*,*S*)-2b isomer, 14.5.

**(*S*,*S*)-2b major isomer (free base):** $R_f$ = 0.45 (heptanes/EtOAc/$NH_4OH$, 75:20:5). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31–7.20 (m, 5 H), 3.88–3.84 (q, $J$ = 6.4 Hz, 1 H), 2.37–2.31 (m, 1 H), 1.64–1.57 (m, 1 H), 1.43–1.13 (m, 7 H), 1.04 (s, 1 H), 0.90–0.88 (d, $J$ = 6.4 Hz, 3 H), 0.81–0.77 (t, $J$ = 8.4 Hz, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 146.7, 128.2, 126.7, 55.1, 53.7, 43.9, 27.3, 25.0, 24.6, 23.4, 22.7, 9.8 ppm. Anal. Calcd (%) for $C_{15}H_{26}ClN$: C, 70.42; H, 10.24; N, 5.48; Found: C, 70.50; H, 10.30; N, 5.44. LRMS (EI): *m/z* (%): 219 (1) [$M^+$], 190 (45), 162 (32), 105 (100), 86 (26), 58 (23). IR (KBr): $\nu_{max}$ 3334, 2957, 2864, 1465, 1155, 1118, 761, 700 cm$^{-1}$.

**CuBr with $Et_2O$ as a solvent:** Reaction details: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv), CuBr (2.87 g, 20.0 mmol, 4.0 equiv), EtMgCl in THF (20.0 mL, 2.0 M, 40.0 mmol, 8.0 equiv), $BF_3{\cdot}OEt_2$ (2.54 mL, 20.0 mmol, 4.0 equiv), $Et_2O$ (44.0 mL, 0.08 M); 80% *de*. 25% (GC area %) starting material remained unreacted. The isolated yield was not recorded.

**(3S)-2-methyl-*N*-((S)-1-phenylethyl)heptan-3-amine (2c):**




**2c**

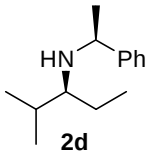
**CuBr with $Et_2O$ as a solvent:** Reaction details: Isobutyraldehyde (0.45 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), *n*-BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), $Et_2O$ (44.0 mL, 0.08 M); 92% *de*. Purification by silica

gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 94:4:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.04 g, 77% yield). The major (*S*,*S*) diastereomer was isolated in pure form by further flash chromatography (hexanes/EtOAc/$NH_4OH$, 97:1:2). GC (program C, see General Experimental Details): retention time [min]: major (*S*,*S)*-2c isomer, 13.56; minor (*R*,*S*)-2c isomer, 13.92.

**(*S*,*S*)-2c major isomer (free base):** $R_f$ = 0.50 (hexanes/EtOAc/$NH_4OH$, 90:8:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31-7.19 (m, 5 H), 3.84 (q, $J$ = 6.4 Hz, 1 H), 2.16-2.14 (m, 1 H), 1.90-1.83 (m, 1 H), 1.36-1.05 (m, 10 H), 0.87-0.79 (m, 9 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.6, 128.2, 126.7, 126.6, 59.0, 55.2, 29.9, 29.0, 28.7, 24.8, 22.8, 18.9, 16.9, 14.0 ppm. This compound has been previously characterized, see reference 11c of the main text.

**CuBr with THF as a solvent:** Reaction details: Isobutyraldehyde (0.45 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), *n*-BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), THF (39.0 mL, 0.09 M); 84% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 94:4:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.07 g, 79% yield).

**(3S)-2-methyl-*N*-((S)-1-phenylethyl)pentan-3-amine (2d):**



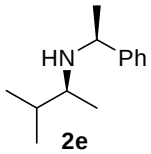

**2d**

**CuBr with THF as a solvent:** Reaction details: Isobutyraldehyde (0.45 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), EtMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.91 mL, 15.0 mmol, 3.0 equiv), THF (39.0 mL, 0.09 M); 86% *ee*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 94:4:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.03 g, 85% yield). The major (*S*,*S*) diastereomer was isolated in pure form by further flash chromatography (hexanes/EtOAc/$NH_4OH$, 96:2:2). GC (program D, see General Experimental Details): retention time [min]: mixture of diastereomers 2d, 11.0 min. The diastereomer does not separate on non chiral GC. After the removal of chiral auxiliary, the *ee* was determined by chiral GC (program I, see General Experimental Details) analysis of the trifluoroacetyl derivative of primary amine.

**(*S*,*S*)-2d major isomer (free base):** $R_f$ = 0.49 (hexane/ EtOAc/$NH_4OH$, 88:10:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31-7.19 (m, 5 H), 3.85 (q, $J$ = 6.4 Hz, 1 H), 2.11-2.07 (m, 1 H), 1.89-1.81 (m, 1 H), 1.36-1.07 (m, 6 H), 0.87-0.78 (m, 9 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.7, 128.1, 126.7, 126.6, 60.9, 55.2, 28.9, 24.7, 22.9, 18.8, 17.1, 10.9 ppm. Anal. Calcd (%) for $C_{14}H_{24}ClN$: C, 69.54; H, 10.00; N, 5.79; Found: C, 69.67; H, 9.96, N; 5.79. LRMS (EI): m/z (%): 205 (2) [$M^+$], 176 (6), 162 (64), 105 (100), 103 (6), 72 (8), 58 (44). IR (KBr): $\nu_{max}$ 3422, 3025, 2958, 2927, 1464, 1368, 1111, 951, 760, 701, 555 $cm^{-1}$.

**CuBr with $Et_2O$ as a solvent:** Reaction details: Isobutyraldehyde (0.45 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), EtMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.91 mL, 15.0 mmol, 3.0 equiv), $Et_2O$ (39.0 mL, 0.09 M); 80% *ee*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 94:4:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (0.957 g, 80% yield).

**(2S)-3-methyl-*N*-((S)-1-phenylethyl)butan-2-amine (2e):**

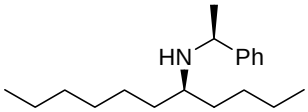



**2e**

**CuBr with THF as a solvent:** Reaction details: Isobutyraldehyde (0.45 mL, 5.0 mmol, 1.0 equiv), CuBr (3.58 g, 25.0 mmol, 5.0 equiv), MeMgCl in THF (16.62 mL, 3.0 M, 50.0 mmol, 10.0 equiv), $BF_3{\cdot}OEt_2$ (3.18 mL, 25.00 mmol, 5.00 equiv), THF (44.0 mL, 0.08 M); 87% de. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 93:5:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (0.88 g, 78% yield). GC (program E, see General Experimental Details): retention time [min]: major (S,S)-2e isomer, 11.19; minor (R,S)- 2e isomer, 11.01.

**(*S*,*S*)-2e major isomer (free base):** $R_f$ = 0.60 (hexanes/EtOAc/$NH_4OH$, 88:10:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.32-7.21 (m, 5 H), 3.85 (q, $J$ = 6.4 Hz, 1 H), 2.44-2.40 (m, 1 H), 1.81-1.74 (m, 1 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.13 (br s, 1 H), 0.86-0.82 (m, 9 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.7, 128.3, 126.6, 126.5, 55.1, 54.9, 30.9, 24.6, 19.5, 16.35, 16.2 ppm. The (*R*,*R*)-isomer of this compound has been previously characterized (see reference 20 of the main text).

**(5S)-*N*-((S)-1-phenylethyl)undecan-5-amine (2f):**



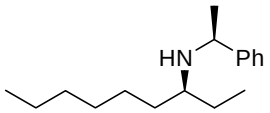

**2f**

**CuBr with $Et_2O$ as a solvent:** Reaction details: Heptaldehyde (0.67 mL, 5.0 mmol, 1.00 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), *n*-BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), $Et_2O$ (44.0 mL, 0.08 M); 86% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.32 g, 85% yield). GC (program F, see General Experimental Details): retention time [min]: major (*S*,*S)*-2f isomer, 42.36; minor (*R*,*S*)-2f isomer, 41.27. The major diastereomer does not separate either by chromatography or by recrystallization.

**Mixture of diastereomers (free base):** $R_f$ = 0.55 (hexanes/ EtOAc/$NH_4OH$, 84:14:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33-7.20 (m, 5 H), 3.86 (q, $J$ = 6.4 Hz, 1 H), 2.32-2.27 (m, 1 H), 1.34-1.12 (m, 20 H), 0.90-0.82 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.4, 128.2, 126.6, 54.9, 53.9, 34.4, 33.6, 31.8, 29.6, 27.9, 25.1, 24.8, 22.8, 22.6, 14.1, 14.0 ppm. IR (KBr): $\nu_{max}$ 3444, 3025, 2957, 2856, 1603, 1466, 1368, 1118, 909, 700, 556 $cm^{-1}$.

**CuBr with THF as a solvent:** Reaction details: Heptaldehyde (0.67 mL, 5.0 mmol, 1.00 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), n-BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), THF (39.0 mL, 0.09 M); 82% de. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.19 g, 87% yield).

**(3S)-*N*-((S)-1-phenylethyl)nonan-3-amine (2g):**




**2g**

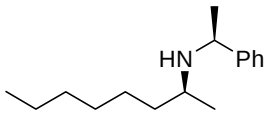
**CuBr with THF as a solvent:** Reaction details: Heptaldehyde (0.67 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), EtMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.91 mL, 15.0 mmol, 3.0 equiv), THF (39.0 mL, 0.09 M); 78% de. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt

(1.21 g, 86% yield). The major (S,S) diastereomer was isolated in pure form by repeated recrystallization (in hexanes) of the HCl salt. GC (program D, see General Experimental Details): retention time [min]: major (S,S)-2g isomer, 13.64; minor (R,S)-2g isomer, 13.48.

**(*S*,*S*)-2g major isomer (free base):** $R_f$ = 0.48 (hexanes/EtOAc/$NH_4OH$, 84:14:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.31-7.19 (m, 5 H), 3.86 (q, $J$ = 6.8 Hz, 1 H), 2.29-2.23 (m, 1 H), 1.43-1.17 (m, 16 H), 0.88 (t, $J$ = 6.8 Hz, 3 H), 0.80 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.5, 128.2, 126.6, 55.5, 55.0, 33.1, 31.8, 29.6, 27.1, 25.1, 24.8, 22.6, 14.1, 10.1 ppm. HRMS (70 eV): calcd. for $C_{17}H_{29}N$ [$M^+$] 247.2300; found 247.2293. LRMS (EI): m/z (%): 247 (2) [$M^+$], 232 (7), 218 (45), 162 (58), 114 (30), 105 (100), 58 (28). IR (KBr): $\nu_{max}$ 3425, 3025, 2959, 2856, 1453, 1368, 1210, 1119, 1028, 700, 553 $cm^{-1}$.

**CuBr with $Et_2O$ as a solvent:** Reaction details: Heptaldehyde (0.67 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), EtMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.91 mL, 15.0 mmol, 3.0 equiv), $Et_2O$ (44.0 mL, 0.08 M); 81% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.14 g, 81% yield).

**(2S)-*N*-((S)-1-phenylethyl)octan-2-amine (2h):**

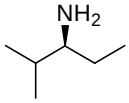



**2h**

**CuBr with THF as a solvent:** Reaction details: Heptaldehyde (0.67 mL, 5.0 mmol, 1.0 equiv), CuBr (4.30 g, 30.0 mmol, 6.0 equiv), MeMgCl in THF (19.95 mL, 3.0 M, 60.0 mmol, 12.0 equiv), $BF_3{\cdot}OEt_2$ (3.82 mL, 30.0 mmol, 6.0 equiv), THF (44.0 mL, 0.08 M); 77% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$, 78:20:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.06 g, 79% yield). GC (program G, see General Experimental Details): retention time [min]: major (*S*,*S)*-2h isomer, 12.65; minor (*R*,*S*)-2h isomer, 12.20.

**(*S*,*S*)-2h major isomer (free base):** $R_f$ = 0.54 (hexanes/EtOAc/$NH_4OH$, 68:30:2). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33-7.20 (m, 5 H), 3.88 (q, $J$ = 6.4 Hz, 1 H), 2.53-2.46 (m, 1 H), 1.34-1.20 (m, 14 H), 0.94 (d, $J$ = 6.4 Hz, 3 H), 0.89 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 146.5, 128.3, 126.6, 126.5, 55.1, 50.1, 36.4, 31.8, 29.5, 25.7, 24.6, 22.6, 21.3, 14.1 ppm. The (*R*,*R*)-isomer of this compound has been previously characterized (see reference 20 of the main text).

**(S)-2-methylpentan-3-amine hydrochloride (3d):**

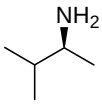


**3d**

The diastereomeric amine mixture (**2d**) (0.408 g, 2.0 mmol) was dissolved in EtOH (5.0 mL, 0.4 M) and AcOH (0.23 mL, 4.0 mmol, 2.0 equiv) was then added and hydrogenolysis was carried out in presence of $Pd(OH)_2/C$ (0.14 g, 5.0 mol %) at 4.1 bar (60 psi) of hydrogen pressure at room temperature. After 6 h, the catalyst was filtered through celite and the celite was washed with EtOH (2 × 10 mL). 2.0 M etheral HCl (2.5 mL) was added to the combined filtrate, and then evaporated to dryness to obtain the white solid. The crude product was dissolved in $CH_2Cl_2$ (15 mL) and basified with 2.0 M NaOH to a pH 10-12. The basic aqueous layer was then extracted with $CH_2Cl_2$ (3 × 15 mL), and the combined $CH_2Cl_2$ extracts were then washed with saturated NaCl, dried over $Na_2SO_4$, and filtered. To the filtrate 2.0 M etheral HCl (2.5 mL) was added and this solution was evaporated, followed by high vacuum drying, gave a white solid (0.235 g, 86% yield) in qualitative purity. The trifluoroacetyl derivative of **3d** has an 86% *ee* (chiral GC program I, see General Experimental Details). GC retention time [min]: major (*S*)-**3d** trifluoroacetamide isomer, 6.4; minor (*R*)-**3d** trifluoroacetamide isomer, 7.2.

**3d-HCl salt**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.33 (br s, 3 H), 3.00-2.94 (m, 1 H), 2.11-2.05 (m, 1 H), 1.79-1.71 (m, 2 H), 1.10-1.05 (m, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 59.4, 29.6, 22.8, 18.4, 17.9, 10.2 ppm. The spectroscopic data of the HCl salt of **3d** matched with the reported literature (see reference 6b of the main text).

**(S)-3-methylbutan-2-amine hydrochloride (3e):**



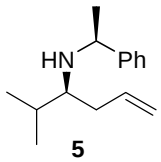
**3e**

The diastereomeric amine mixture (**2e**) (0.382 g, 2.0 mmol) was dissolved in EtOH (5.0 mL, 0.4 M) and AcOH (0.23 mL, 4.0 mmol, 2.0 equiv) was then added and hydrogenolysis was carried out in presence of $Pd(OH)_2/C$ (0.14 g, 5.0 mol %) at 4.1 bar (60 psi) of hydrogen pressure at room temperature. After 6 h, the catalyst was filtered through celite and the celite was washed with EtOH (2 × 10 mL). 2.0 M etheral HCl (2.5 mL) was added to the combined filtrate, and then evaporated to dryness to obtain the white solid. The crude product was dissolved in $CH_2Cl_2$ (15 mL) and basified with 2.0 M NaOH to a pH 10-12. The basic aqueous layer was then extracted with $CH_2Cl_2$ (3 × 15

mL), and the combined $CH_2Cl_2$ extracts were then washed with saturated NaCl, dried over $Na_2SO_4$, and filtered. To the filtrate 2.0 M etheral HCl (2.5 mL) was added and this solution was evaporated, followed by high vacuum drying, gave a white solid (0.215 g, 87% yield) in qualitative purity. The trifluoroacetyl derivative **3e** has an 87% *ee* (chiral GC program J, see General Experimental Details). GC retention time [min]: major (*S*)-**3e** trifluoroacetamide isomer, 59.8; minor (*R*)-**3e** trifluoroacetamide isomer, 64.2.

**3e-HCl salt**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.36 (br s, 3 H), 3.17-3.15 (m, 1 H), 2.04-1.96 (m, 1 H), 1.37-1.35 (m, 3 H), 1.07-1.03 (m, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 53.6, 31.7, 18.8, 17.7, 15.4 ppm. The spectroscopic data of the HCl salt of **3e** matched with the reported literature (see reference 6b of the main text).

**(3S)-2-methyl-*N*-((S)-1-phenylethyl)hex-5-en-3-amine (5):**



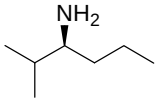

**5**

Under an argon atmosphere, THF (15.0 mL) was added to isobutyraldehyde (0.46 mL, 5.0 mmol, 1.0 equiv) and Ti(O*i*Pr)$_4$ (0.73 mL, 2.5 mmol, 0.5 equiv) with stirring followed by (*S*)-α-MBA (0.71 mL, 5.5 mmol, 1.1 equiv) and stirring was continued for 45 min. Then cooled to -78 °C and stirring continued for another 15 min. Allylmagnesium chloride in THF (8.75 mL, 2 M, 17.5 mmol, 3.5 equiv) was added drop wise by syringe over 10 min. After 1 h the reaction was quenched with 10 mL 1.0 M NaOH and stirred for 30 min. The reaction mixture was then filtered through a bed of celite and the celite subsequently washed with $CH_2Cl_2$ (4 × 20 mL). The combined organic layer was washed with saturated $NH_4Cl$ (2 × 25 mL), then with deionized $H_2O$ (2 × 20 mL), dried over $Na_2SO_4$, filtered, and then evaporated to dryness to obtain the crude product (80% de). Purification by silica gel flash chromatography (hexanes/EtOAc/$NH_4OH$ 93:4:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with etheral HCl to obtain the hydrochloride salt (1.11 g, 87% yield). The major (*S*,*S*) diastereomer was isolated in pure form after further flash chromatography (hexanes/EtOAc/$NH_4OH$, 95.5:0.5:4.0 to 94:1:5). GC (program H, see General Experimental Details): retention time [min]: major (*S*,*S*)-**5** isomer, 23.29; minor (*R*,*S*)-**5** isomer, 23.06.

**(*S*,*S*)-5 major isomer (free base):** $R_f$ = 0.52 (cyclohexanes/EtOAc/$NH_4OH$, 88:10:2). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33-7.20 (m, 5 H), 5.84-5.74 (m, 1 H), 5.06 (m, 2 H), 3.87 (q, *J* = 6.4 Hz, 1 H), 2.19 (m, 3 H), 1.59 (m, 1 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8

Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 146.4, 136.3, 128.2, 126.9, 126.6, 116.6, 59.4, 55.4, 34.8, 30.4, 24.9, 19.0, 18.3 ppm. IR (KBr): $\nu_{max}$ 3429, 2924, 2853, 1637 cm$^{-1}$.

**(S)-2-methylhexan-3-amine hydrochloride (6):**

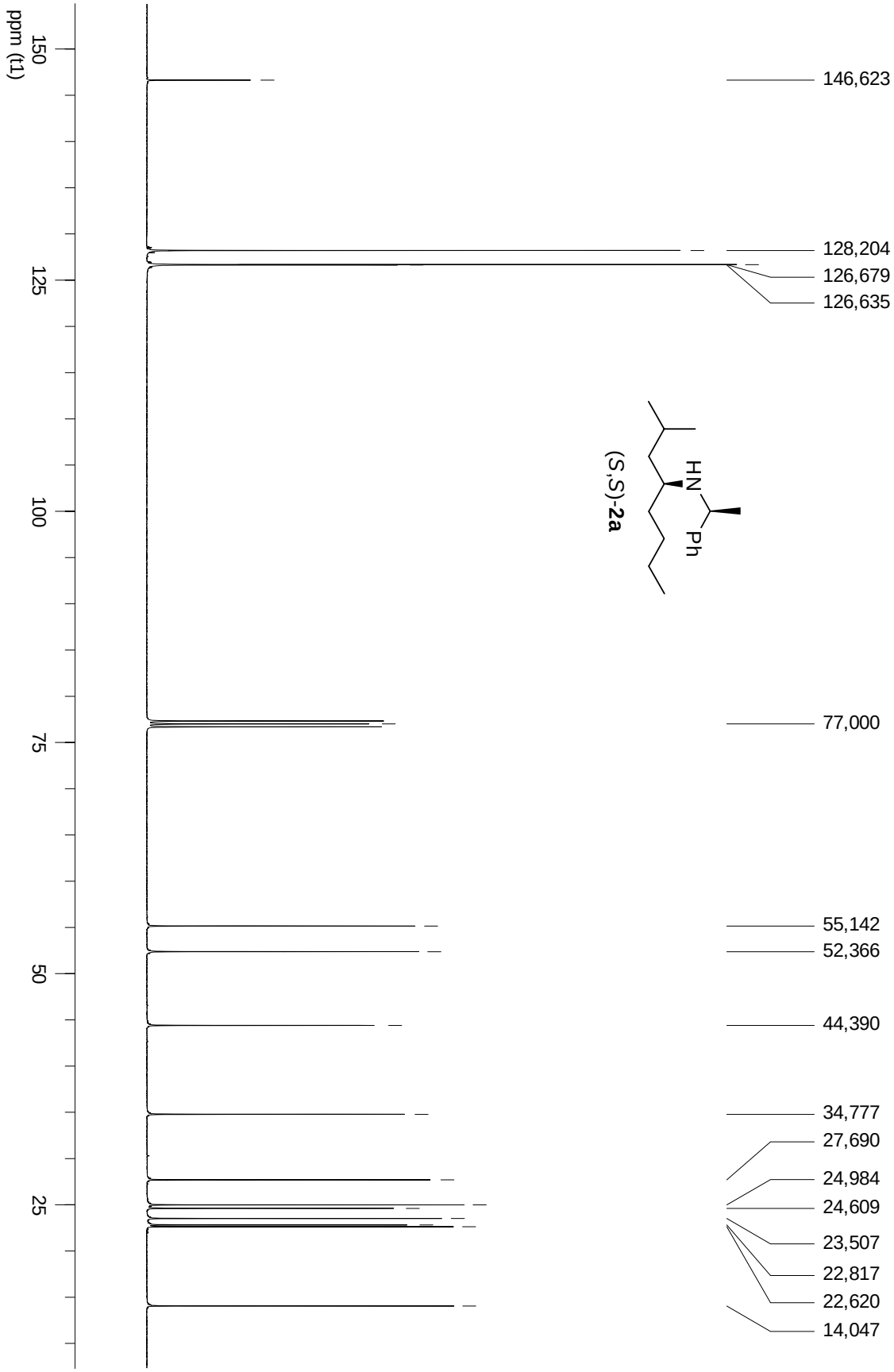


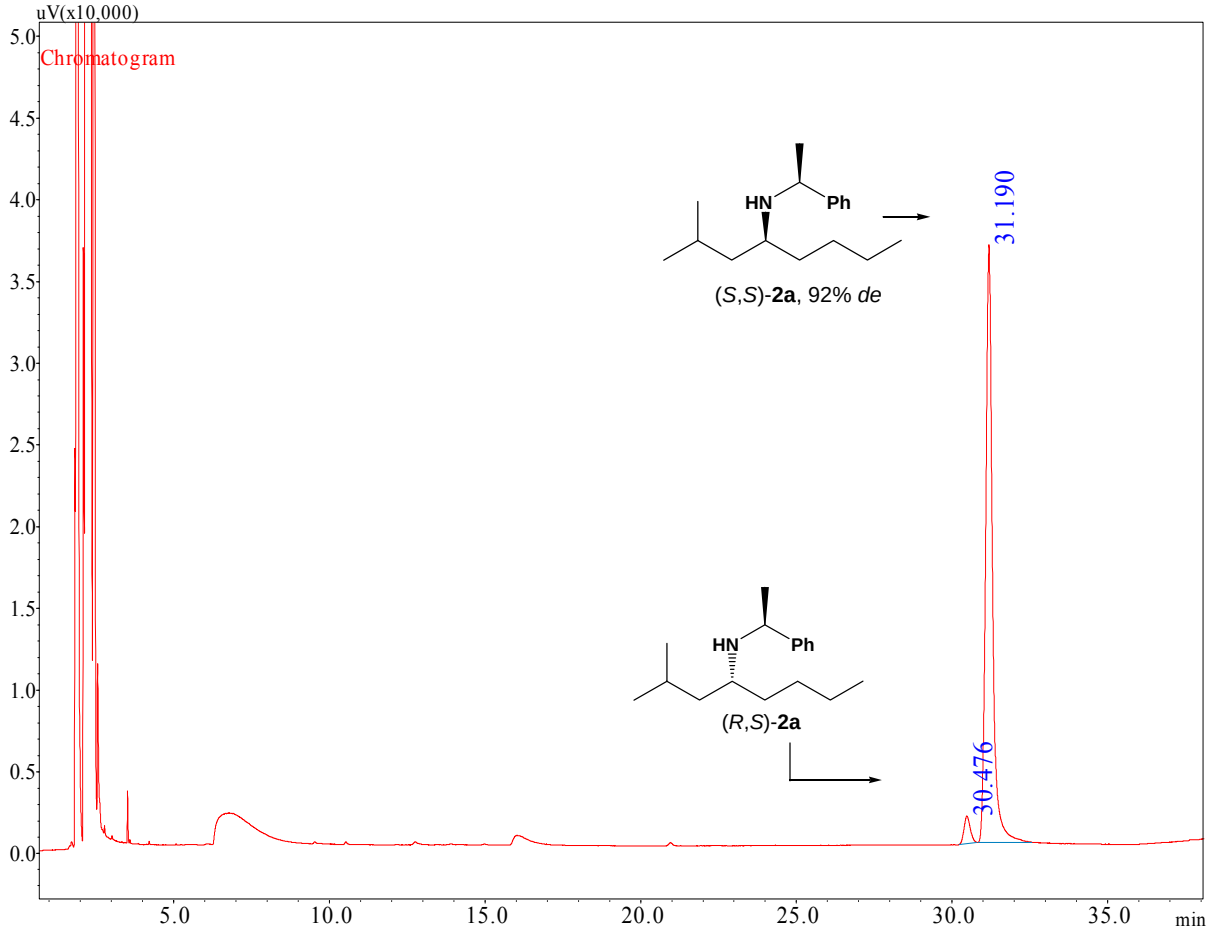

**6**

The diastereomeric amine mixture (**5**) (0.435 g, 2.0 mmol) was dissolved in MeOH (5.0 mL, 0.4 M) and hydrogenolysis was carried out in presence of Pd/C (0.34 g, 4.0 mol %) at 4.1 bar (50 psi) of hydrogen pressure at room temperature. After 5 h, the catalyst was filtered through celite and the celite was washed with MeOH (4 × 10 mL). 4.0 M etheral HCl (2.5 mL) was added to the combined filtrate, and then evaporated to dryness to obtain the oily liquid. The oily liquid was triturated with ether (4 × 5 mL) and evaporated successively for 3-4 times to get a white solid. Further drying in vacuum for 15 h provided a free flowing white solid in quantitative purity (0.292 g, 96% yield). The trifluoroacetyl derivative **6** has an 76% *ee* (chiral GC program K, see General Experimental Details). GC retention time [min]: major (*S*)-**6** trifluoroacetamide isomer, 28.8; minor (*R*)-**6** trifluoroacetamide isomer, 27.5.

**6-HCl salt**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.34 (br s, 3 H), 3.05 (br s, 1 H), 2.07 (m, 1 H), 1.54-1.74 (m, 3 H), 1.44 (m, 1 H), 1.08 (d, $J$ = 6.8 Hz, 3 H), 0.95 (t, $J$ = 6.8 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 57.7, 31.7, 30.0, 19.0, 18.3, 17.9, 13.8 ppm. The (*R*)-isomer of this compound has been previously characterized (see reference 20 of the main text).

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
4.96
1.00
1.02
1.07
12.04
2.00
7,329
7,307
7,296
7,257
7,236
7,215
7,193
3,881
3,865
3,848
3,832
2,382
2,365
2,354
2,337
2,325
1,634
1,617
1,600
1,583
1,550
1,331
1,315
1,292
1,186
1,152
1,120
0,896
0,879
0,847
0,830
0,813
0,778
0,761
-0,000000
HN
Ph
(S,S)-2a

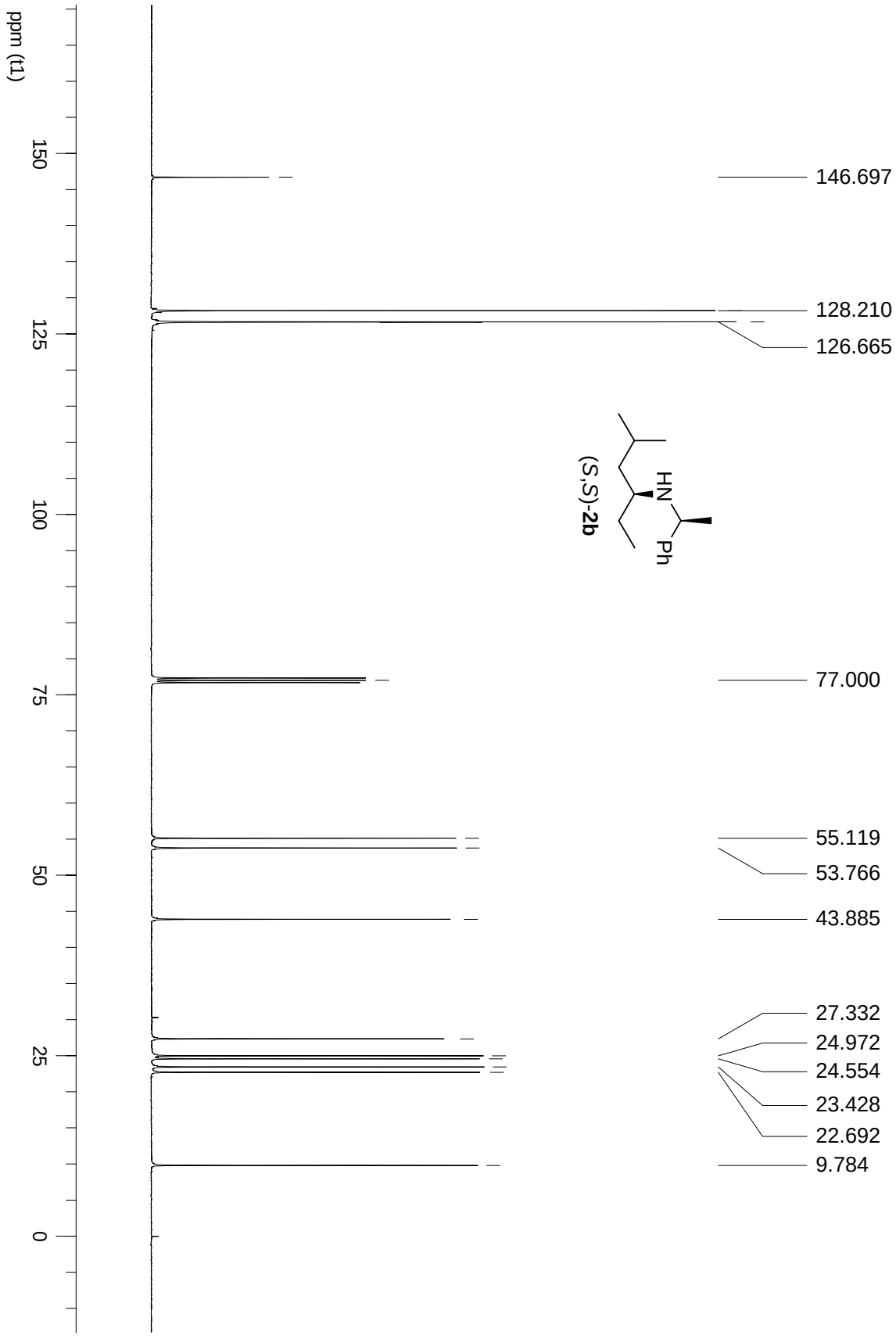

ppm (t1)
150
125
100
75
50
25
146,623
128,204
126,679
126,635
77,000
55,142
52,366
44,390
34,777
27,690
24,984
24,609
23,507
22,817
22,620
14,047
HN
Ph
(S,S)-2a

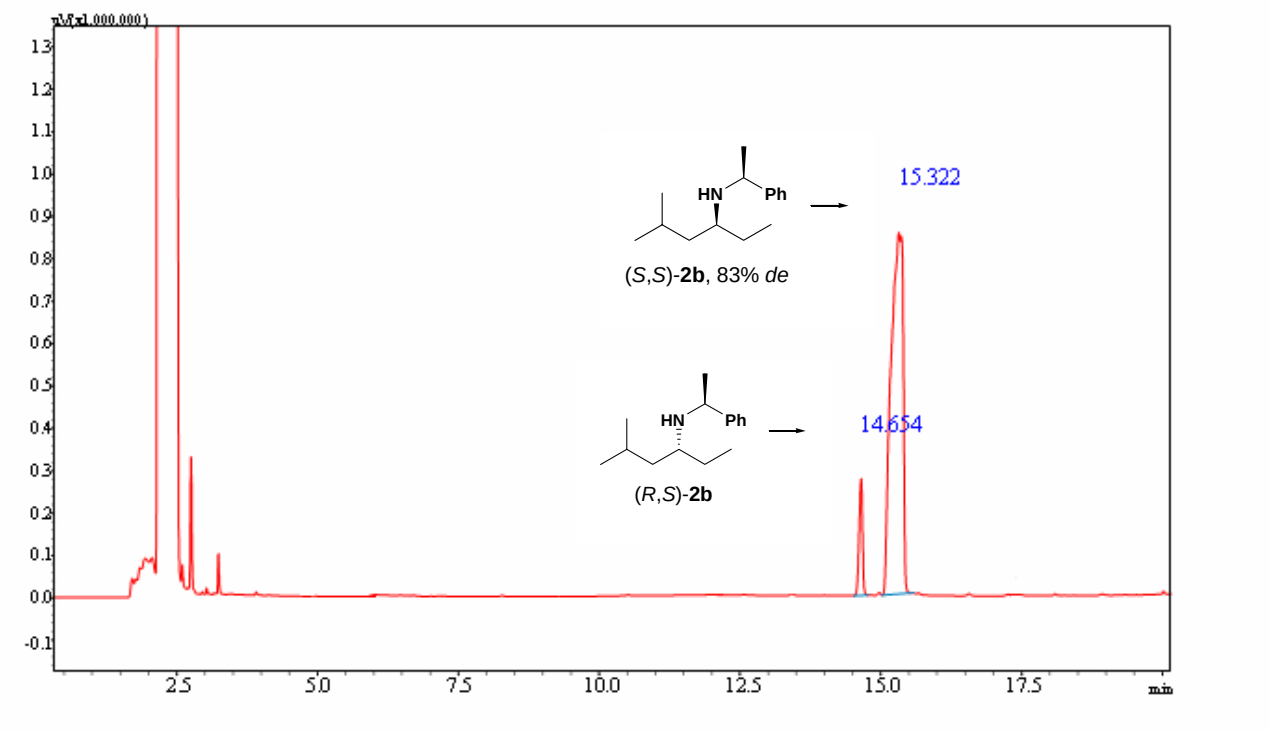



Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 30.476 | 23222.1 | 1677.2 | 4.02083 |
| 2 | 31.190 | 554321.4 | 36526.6 | 95.97917 |

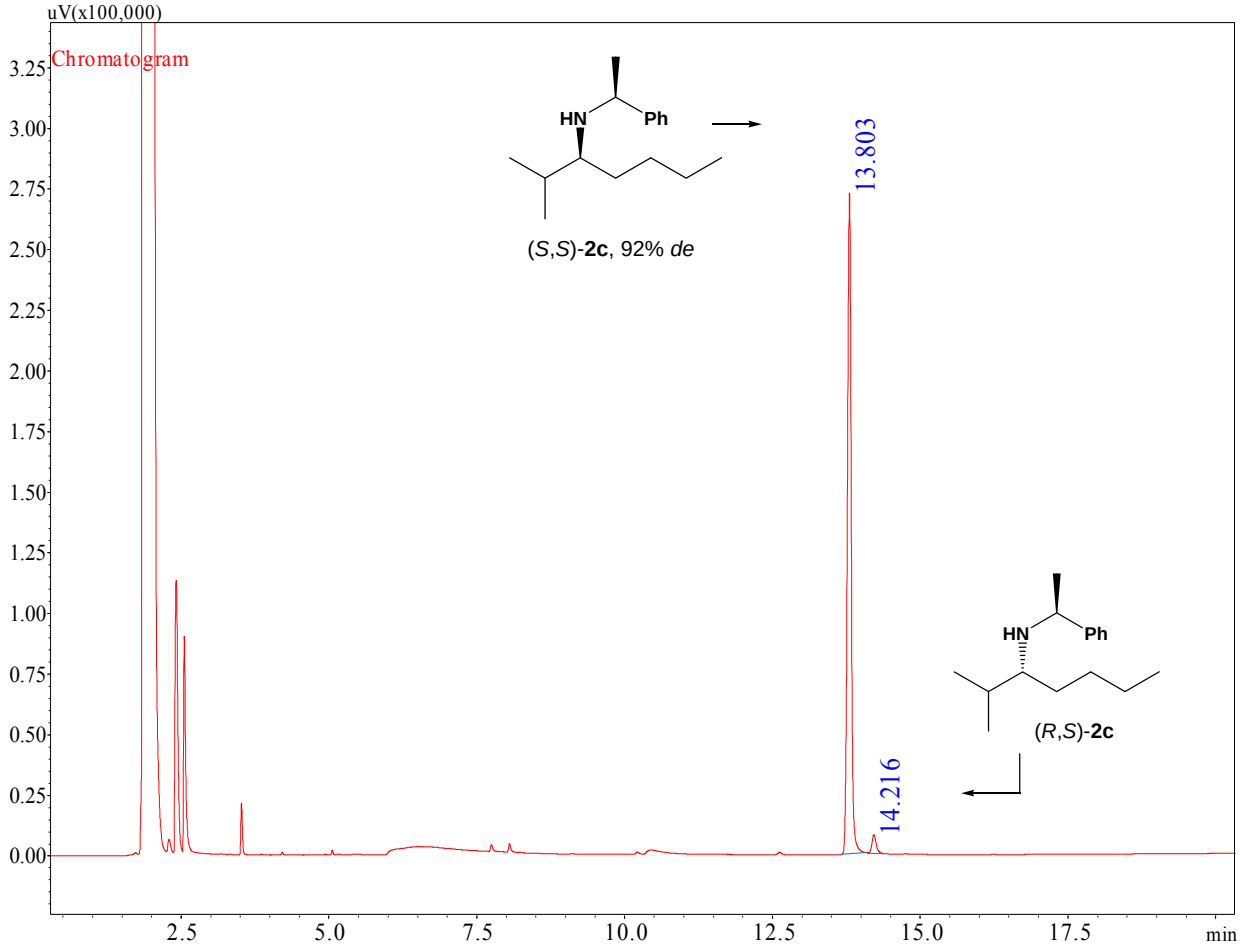
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
4.68
1.00
1.01
1.01
7.26
0.88
3.08
6.10
7.309
7.298
7.231
7.221
7.210
7.202
HN
Ph
(S,S)-2b
3.884
3.868
3.851
3.835
2.366
2.350
2.336
2.321
2.306
1.642
1.626
1.609
1.592
1.575
1.431
1.416
1.399
1.328
1.312
1.180
1.163
1.146
1.129
1.036
0.898
0.882
0.813
0.792
0.774
0.000000


ppm (t1)
150
125
100
75
50
25
0
146.697
128.210
126.665
77.000
55.119
53.766
43.885
27.332
24.972
24.554
23.428
22.692
9.784
HN
Ph
(S,S)-2b




Peak Table-Channel 1

| Peak | Ret time | Area | Height | Conc |
|---|---|---|---|---|
| 1 | 14.654 | 1163061.8 | 275265.4 | 8.42008 |
| 2 | 15.322 | 12649891.1 | 852571.3 | 91.57992 |




Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 13.803 | 1218211.3 | 272265.8 | 97.03259 |
| 2 | 14.216 | 37254.8 | 7544.0 | 2.96741 |

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
4.79
1.00
1.02
1.03
6.20
9.20
7,317
7,309
7,303
7,283
7,231
7,224
7,217
7,203
7,195
HN
Ph
(S,S)-2d
3,873
3,856
3,840
3,824
2,114
2,104
2,093
2,083
2,073
1,898
1,881
1,870
1,863
1,853
1,846
1,836
1,819
1,360
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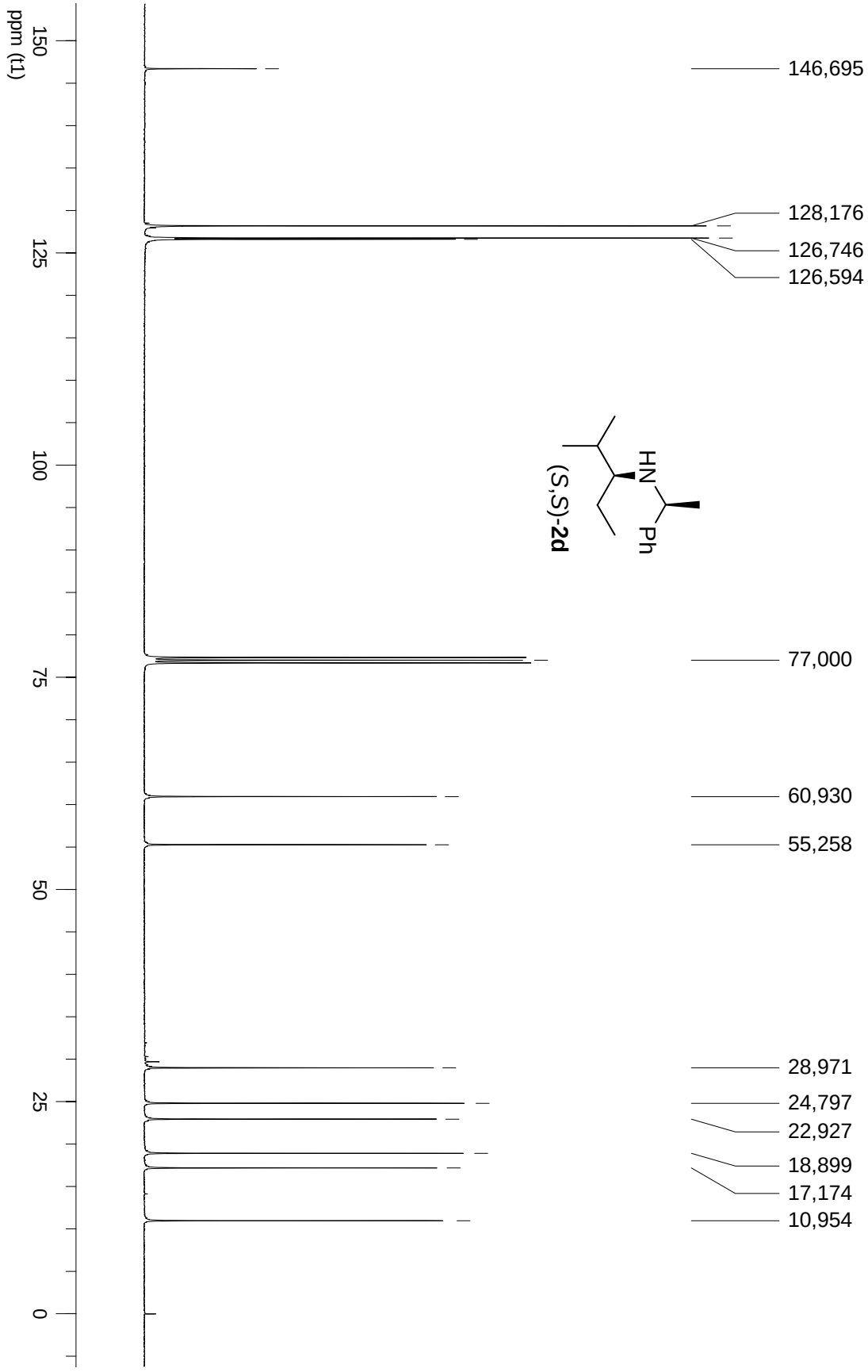
1,091
1,072
0,875
0,857
0,823
0,806


ppm (t1)
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75
50
25
0
146,695
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126,746
126,594
77,000
60,930
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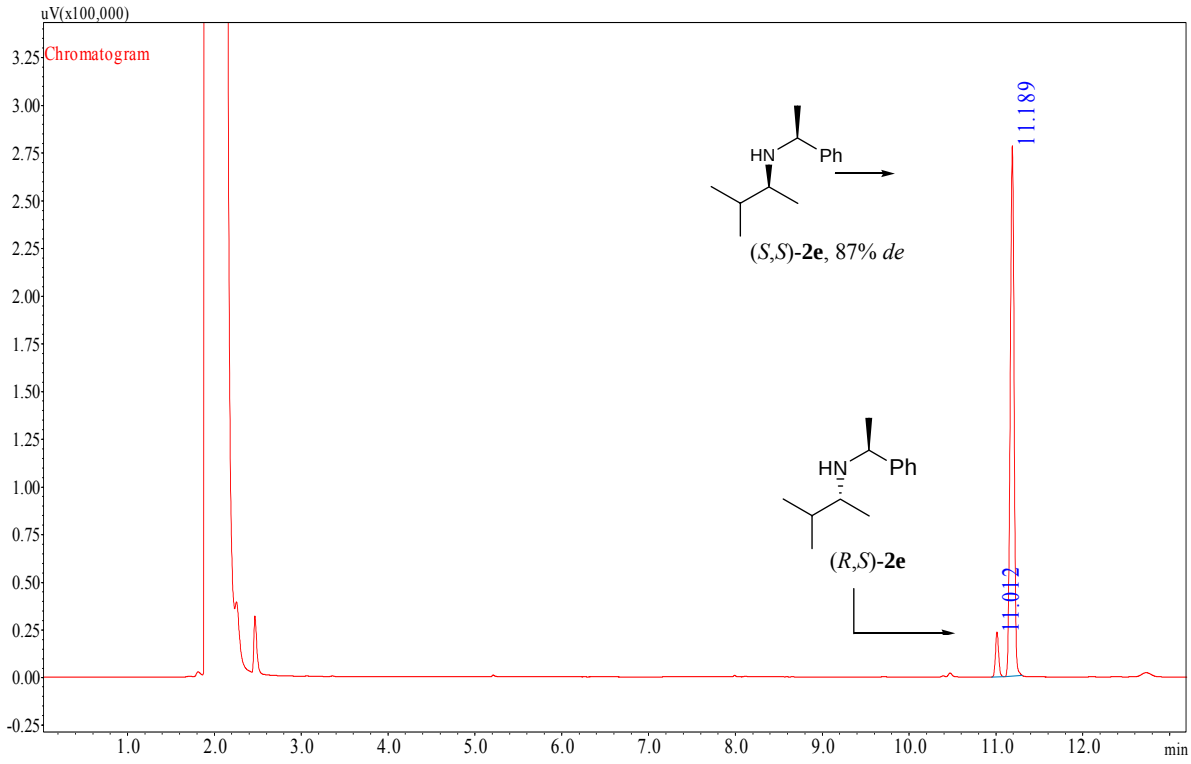
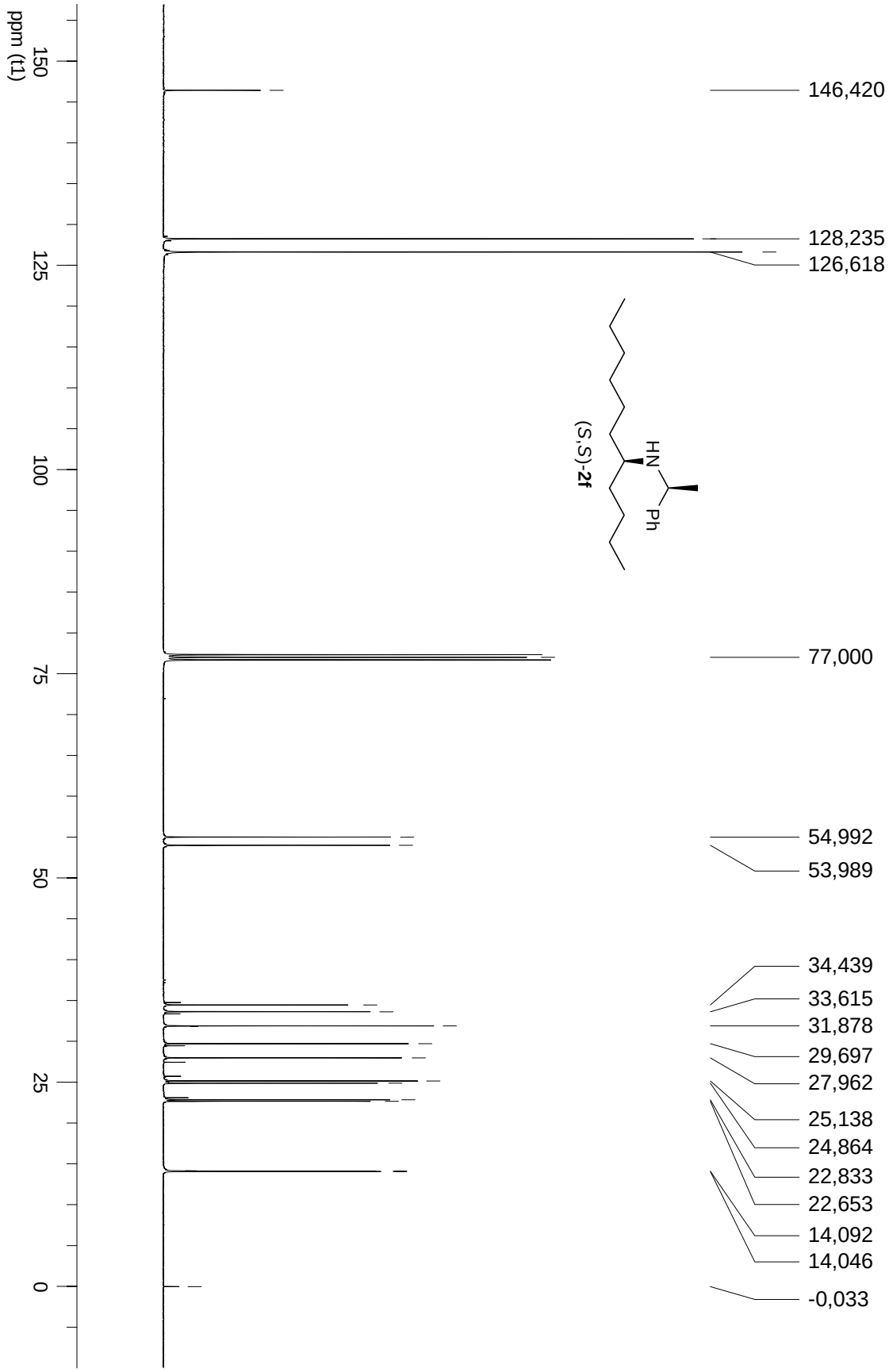
28,971
24,797
22,927
18,899
17,174
10,954
HN
Ph
(S,S)-2d




Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 11.012 | 58858.0 | 23433.5 | 6.38082 |
| 2 | 11.189 | 863562.9 | 277514.5 | 93.61918 |

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
4.95
1.00
1.02
20.02
6.05
7,333
7,313
7,296
7,279
7,258
7,235
7,219
7,203
3,882
3,865
3,849
3,833
2,321
2,306
2,294
2,280
2,267
1,399
1,389
1,332
1,316
1,261
1,201
1,185
1,168
1,153
1,144
1,121
0,900
0,884
0,867
0,852
0,835
0,817
-0,00000
HN
Ph
(S,S)-2f


ppm (t1)
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100
75
50
25
0
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128,235
126,618
77,000
54,992
53,989
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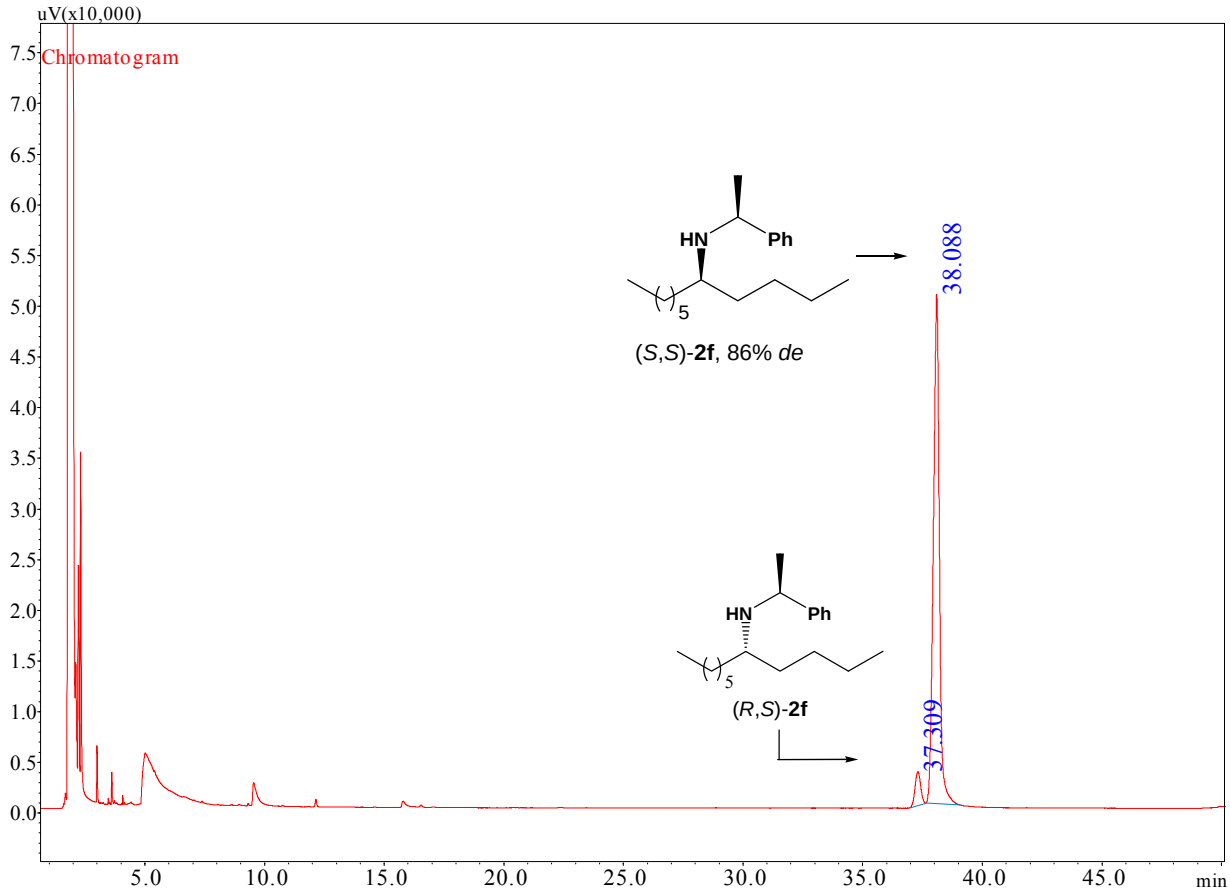
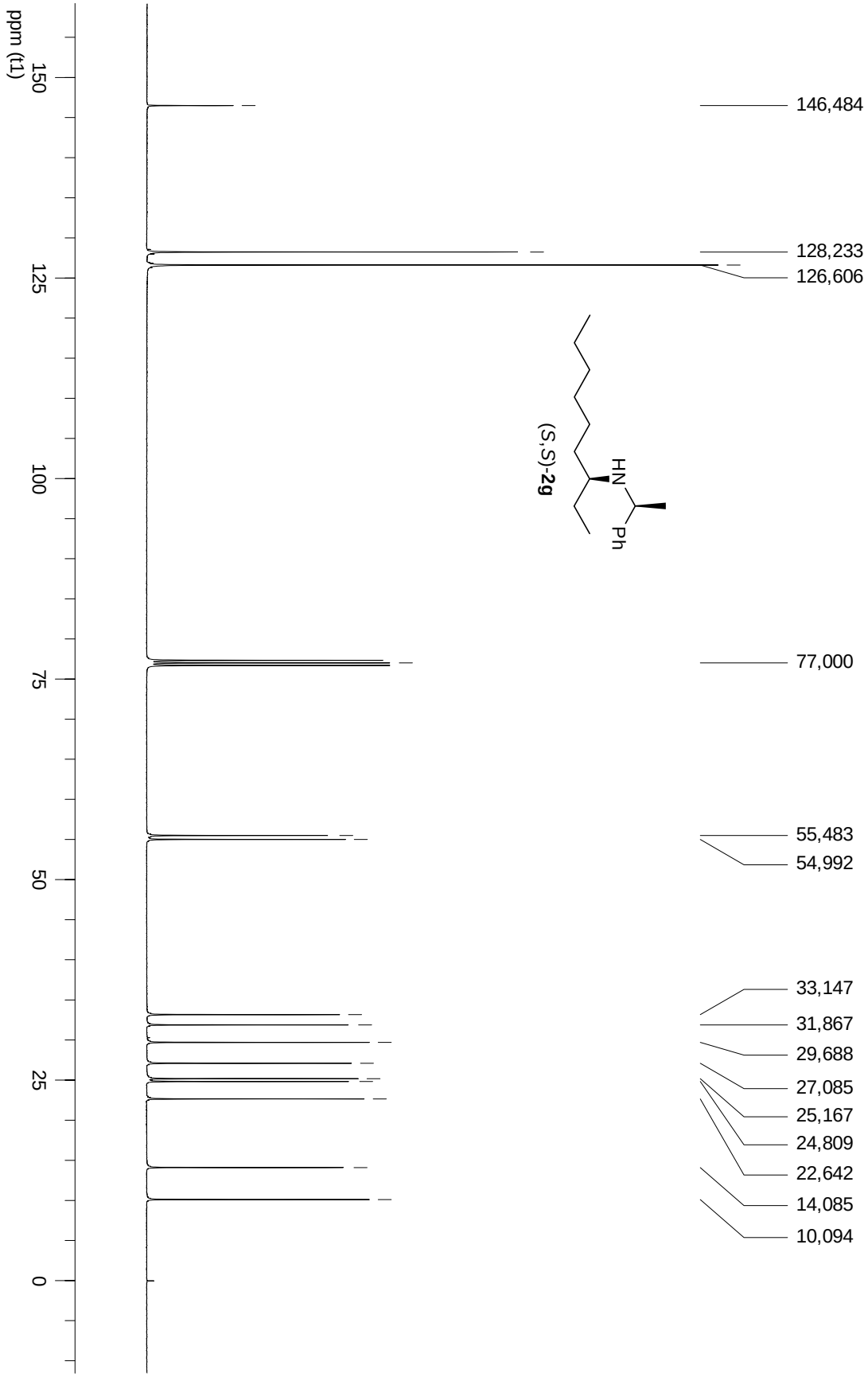
33,615
31,878
29,697
27,962
25,138
24,864
22,833
22,653
14,092
14,046
-0,033
(S,S)-2f
HN
Ph




| Peak Table-Channel 1 | | | | |
|---|---|---|---|---|
| **Peak** | **Ret. Time** | **Area** | **Height** | **Conc.** |
| 1 | 37.309 | 54288.8 | 3344.2 | 5.83422 |
| 2 | 38.088 | 876235.8 | 50239.5 | 94.16578 |

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
4.79
1.00
1.00
16.00
2.92
3.00
7,314
7,309
7,301
7,256
7,241
7,233
7,228
7,219
7,205
7,198
(S,S)-2g
HN
Ph
3,888
3,871
3,855
3,838
2,290
2,275
2,262
2,248
2,233
1,432
1,412
1,378
1,360
1,333
1,316
1,262
1,190
1,174
0,901
0,884
0,867
0,819
0,800
0,782
0,0000000


ppm (t1)
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100
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25
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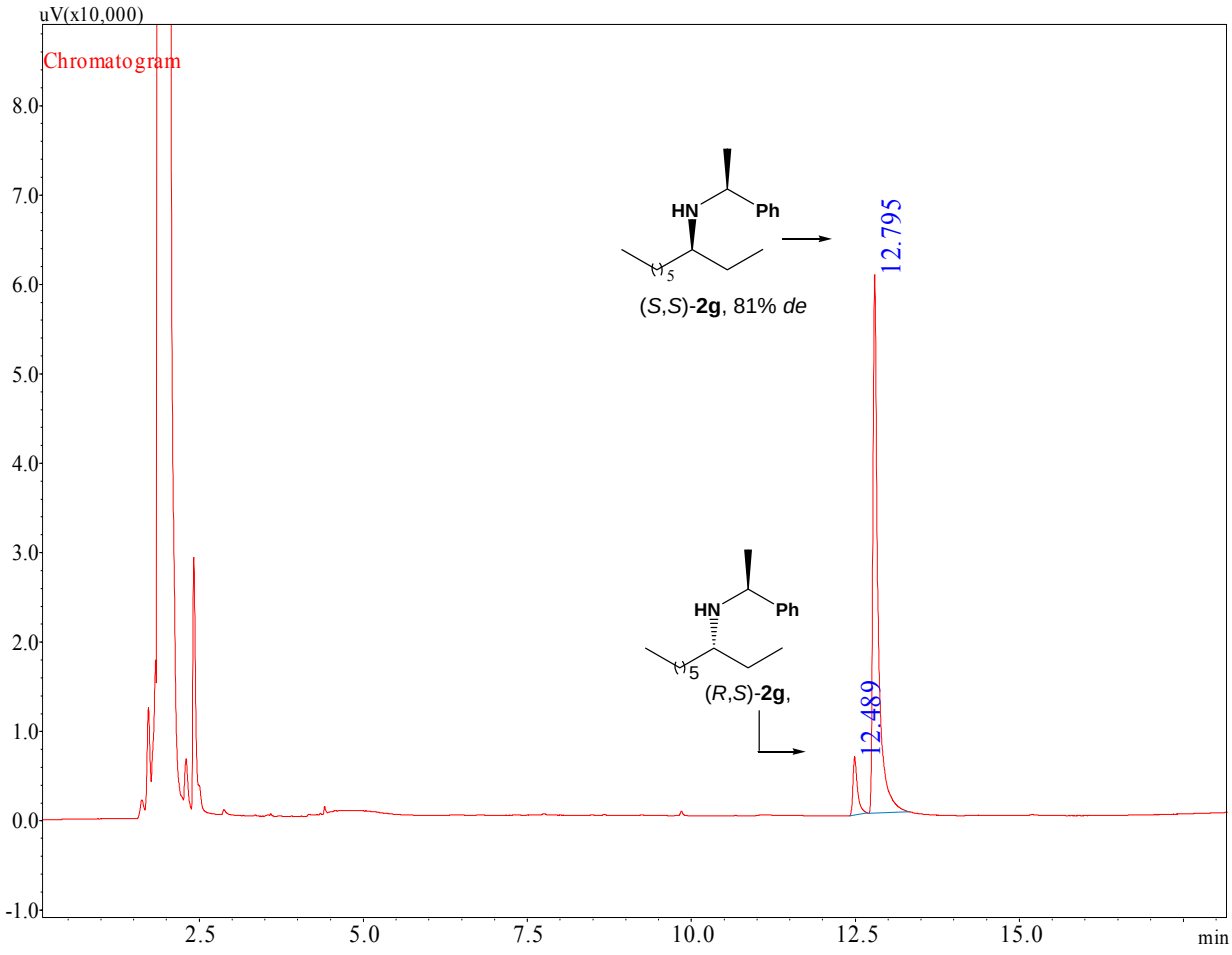
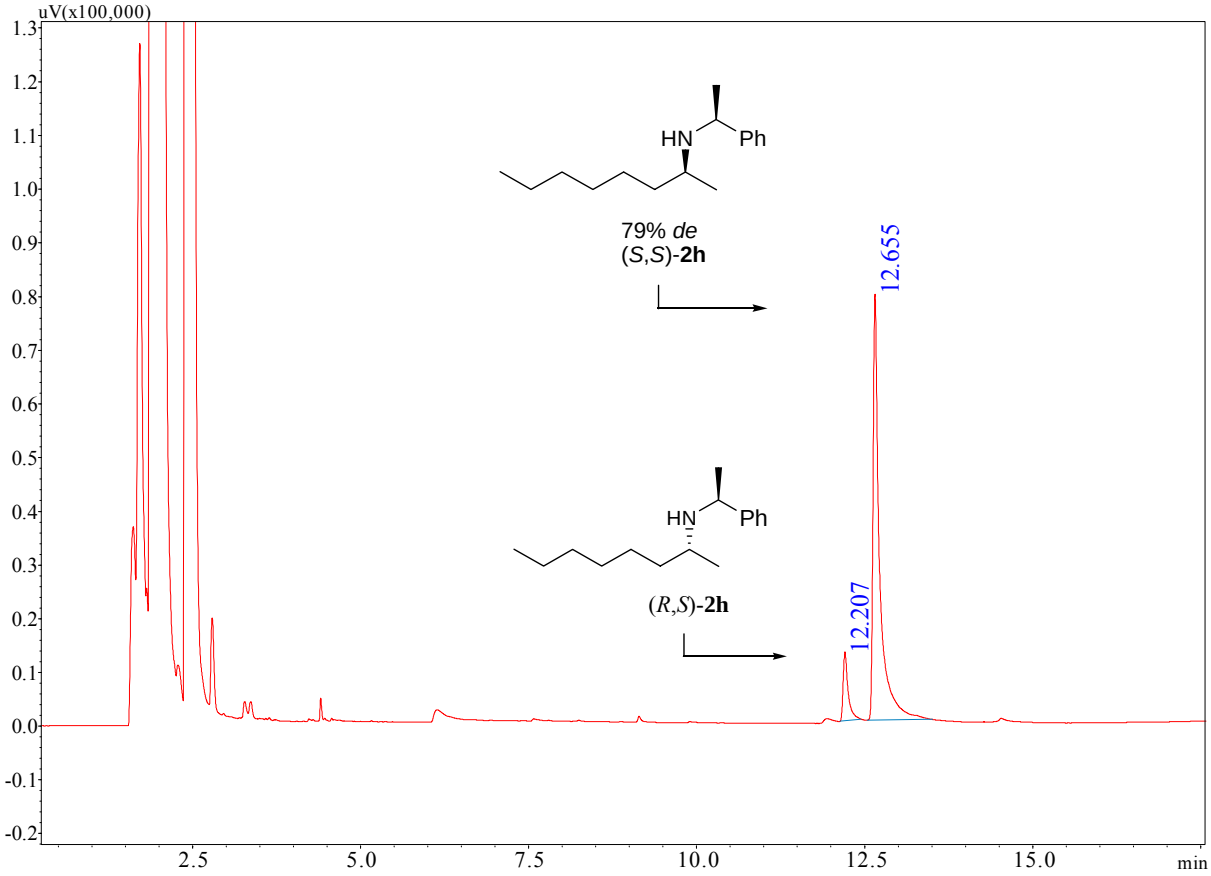
126,606
77,000
55,483
54,992
33,147
31,867
29,688
27,085
25,167
24,809
22,642
14,085
10,094
(S,S)-2g
HN
Ph



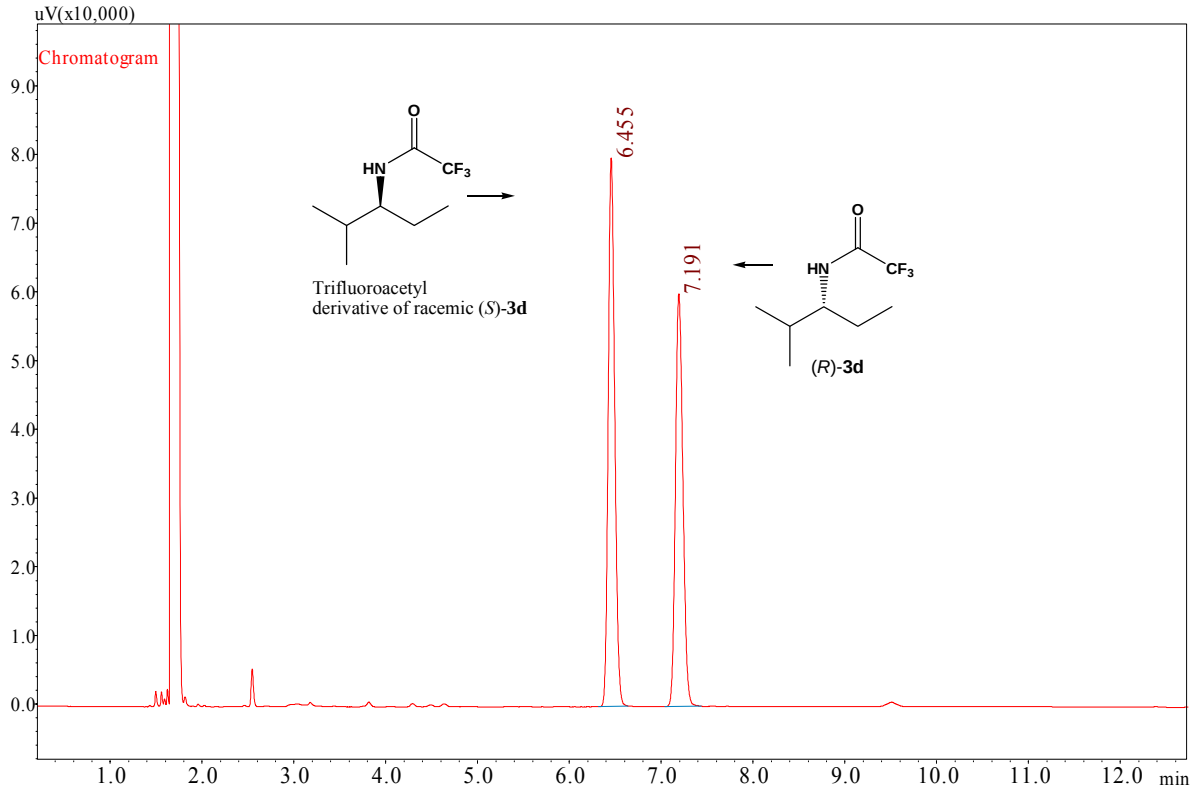

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 12.489 | 30928.5 | 6460.8 | 8.57061 |
| 2 | 12.795 | 329939.1 | 60135.3 | 91.42939 |



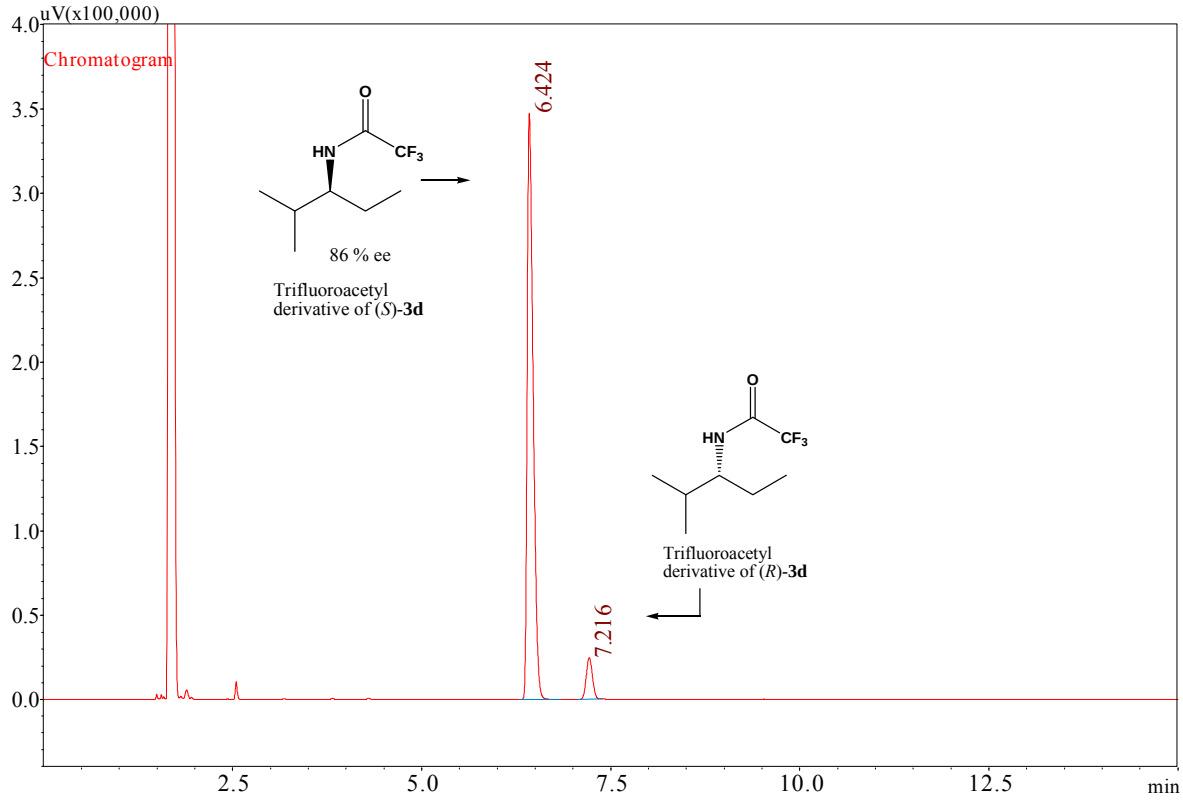

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 12.207 | 64893.2 | 12748.5 | 10.58357 |
| 2 | 12.655 | 548257.2 | 79191.3 | 89.41643 |



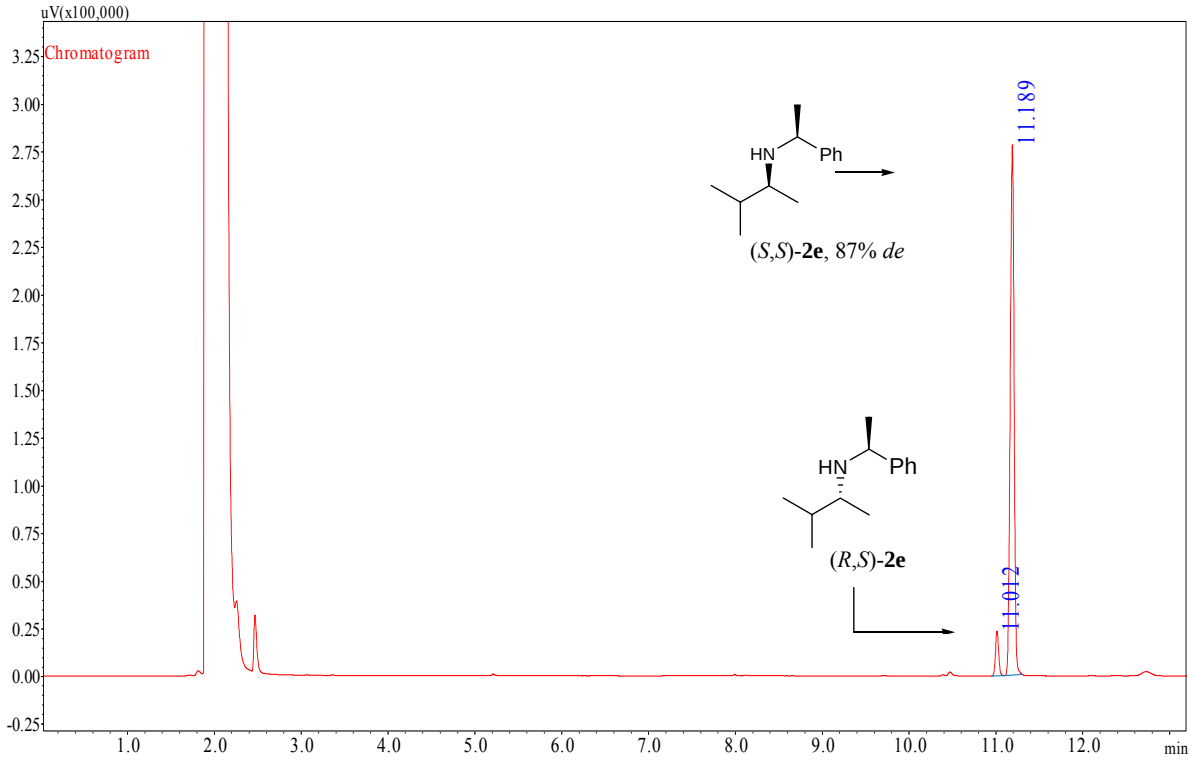

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 6,455 | 392818 | 79822 | 53,618 |
| 2 | 7,191 | 339809 | 60060 | 46,382 |



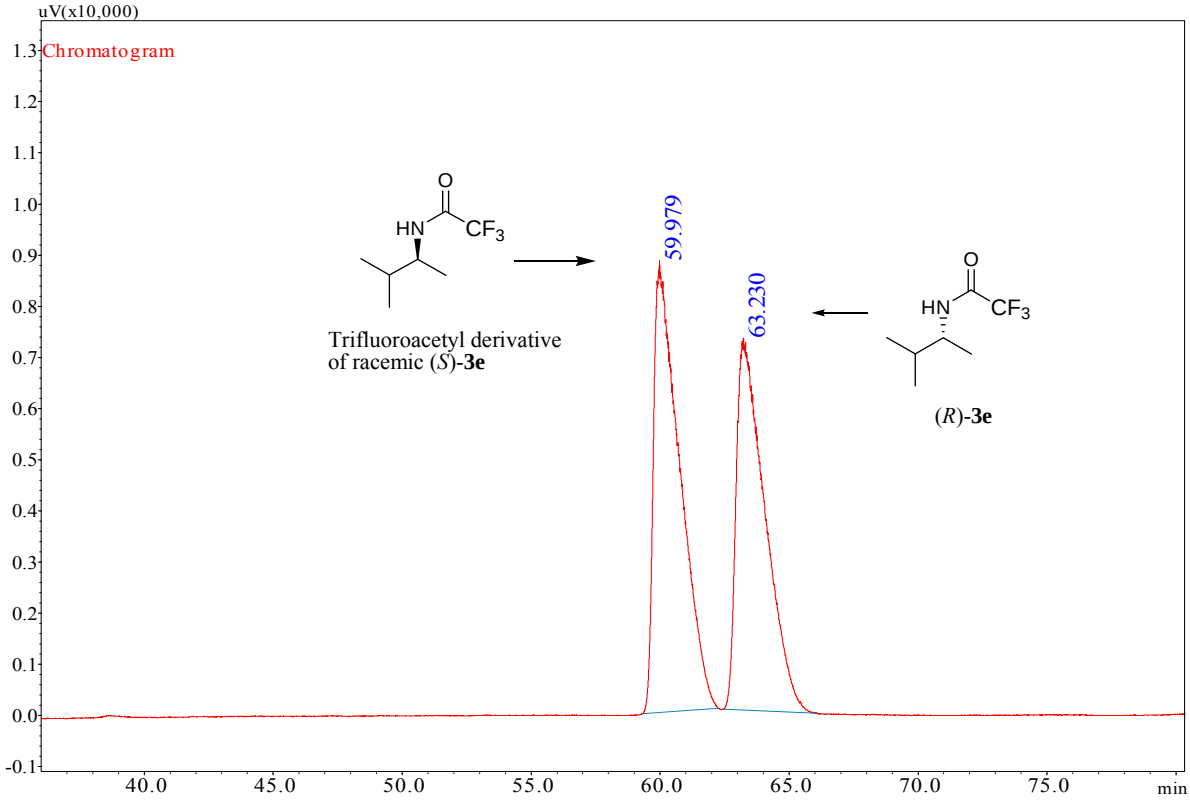

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 6.424 | 1898520.3 | 347227.0 | 93.143 |
| 2 | 7.216 | 139772.7 | 24695.6 | 6.857 |



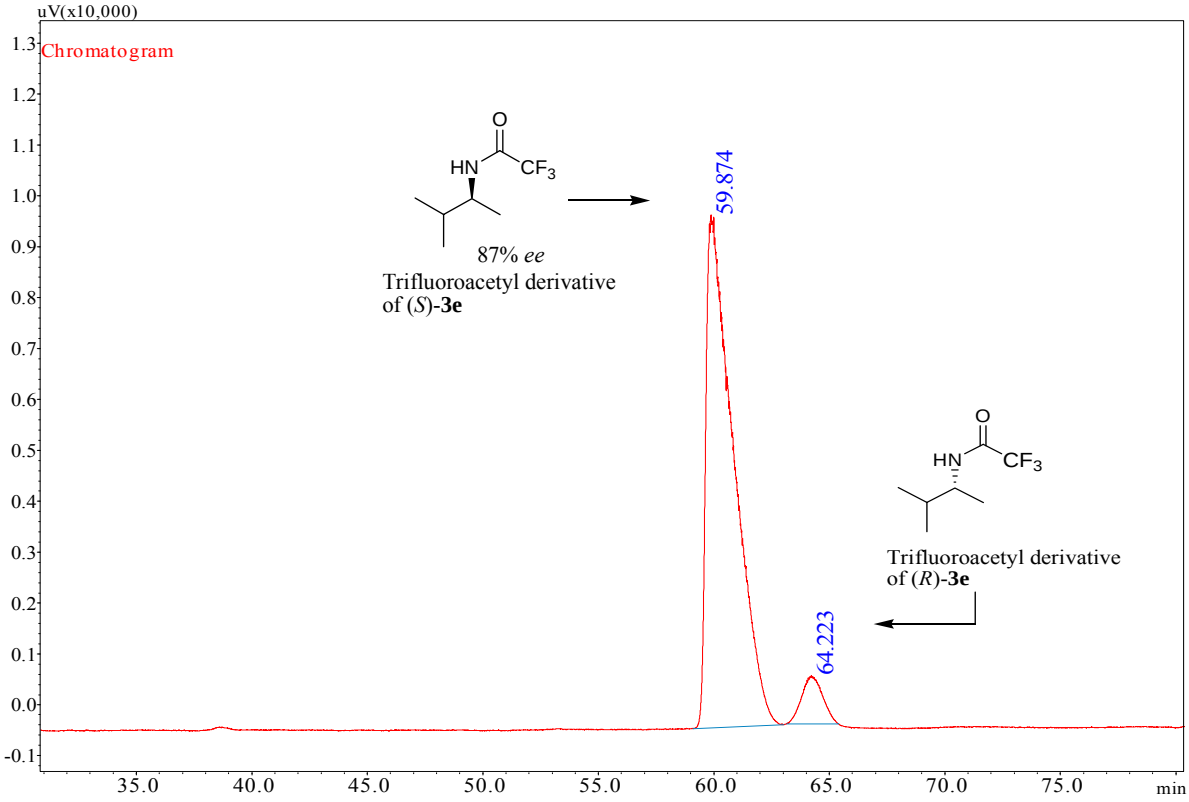

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 11.012 | 58858.0 | 23433.5 | 6.38082 |
| 2 | 11.189 | 863562.9 | 277514.5 | 93.61918 |




Peak Table-Channel 1

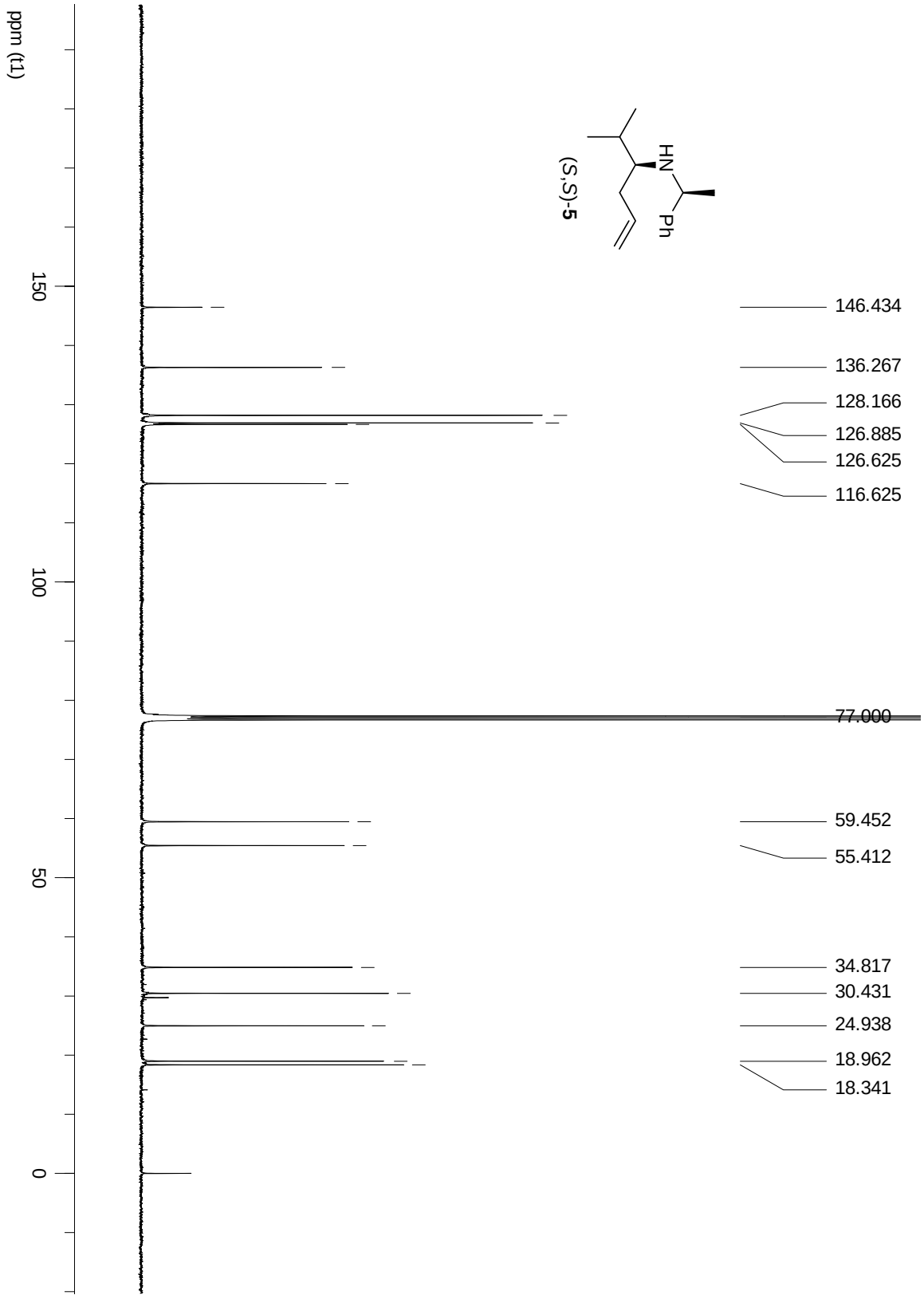
| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 59.979 | 619574.1 | 8819.5 | 52.51583 |
| 2 | 63.230 | 560211.3 | 7265.3 | 47.48417 |

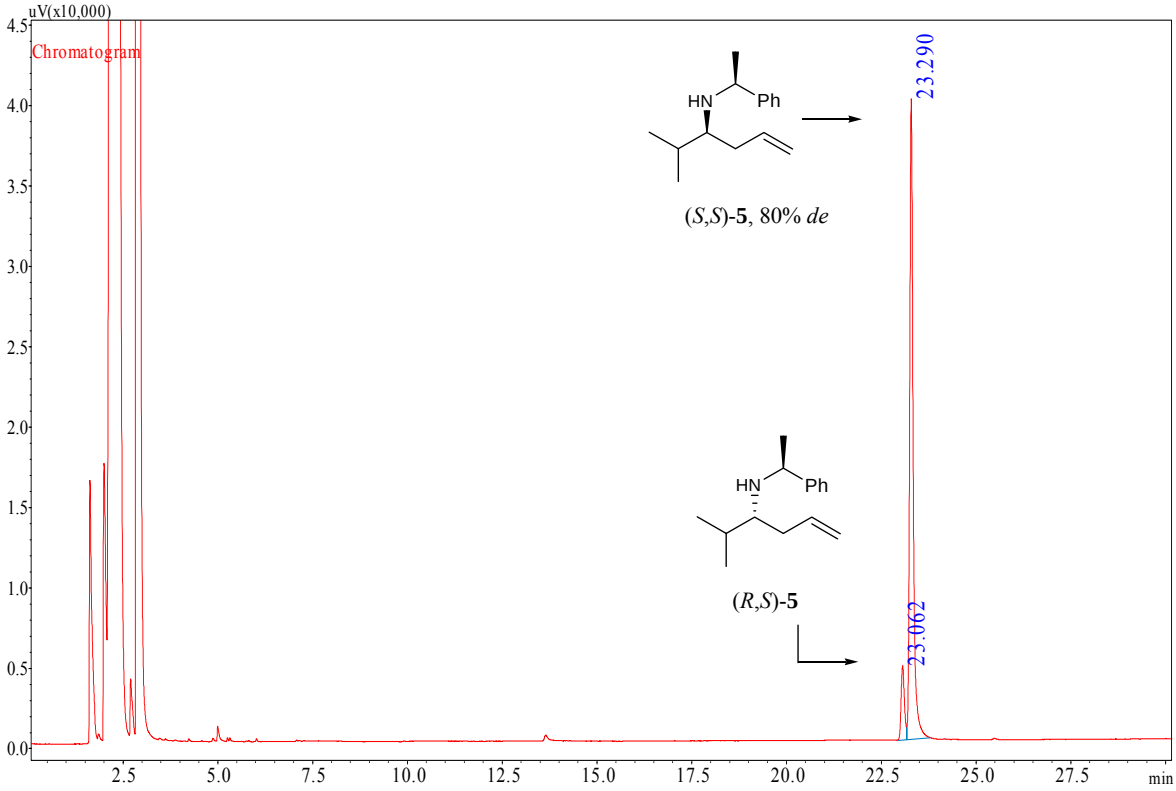



Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 59.874 | 837320.2 | 10066.2 | 93.30537 |
| 2 | 64.223 | 60077.5 | 957.8 | 6.69463 |

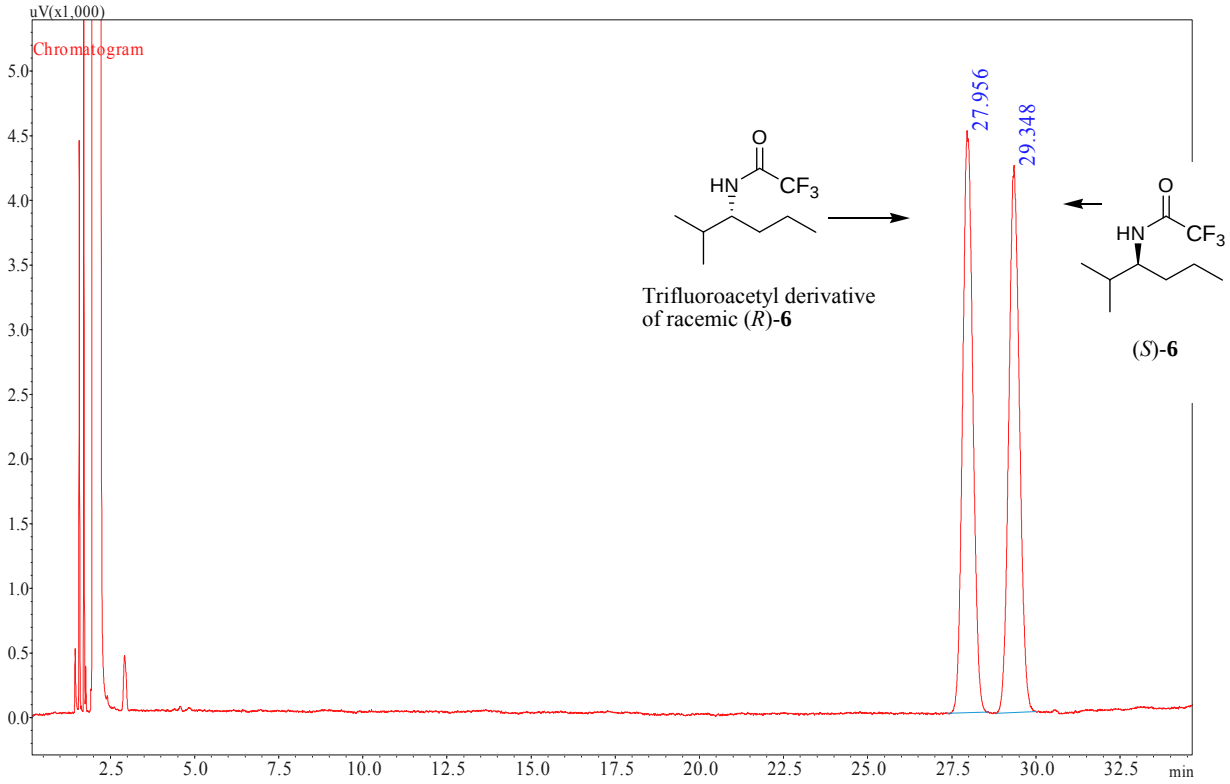
ppm (t1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
4.96
0.95
1.93
1.00
3.07
1.08
3.03
3.07
2.09
(S,S)-5
HN
Ph
7.334
7.317
7.300
7.281
7.256
7.214
7.198
5.837
5.820
5.795
5.778
5.752
5.735
5.086
5.065
5.041
3.891
3.875
3.858
3.842
2.234
2.216
2.189
2.179
2.159
2.142
1.629
1.595
1.583
1.567
1.550
1.309
1.293
0.858
0.841
0.802
0.785
-0.000000


ppm (t1)
150
100
50
0
(S,S)-5
HN
Ph
146.434
136.267
128.166
126.885
126.625
116.625
77.000
59.452
55.412
34.817
30.431
24.938
18.962
18.341



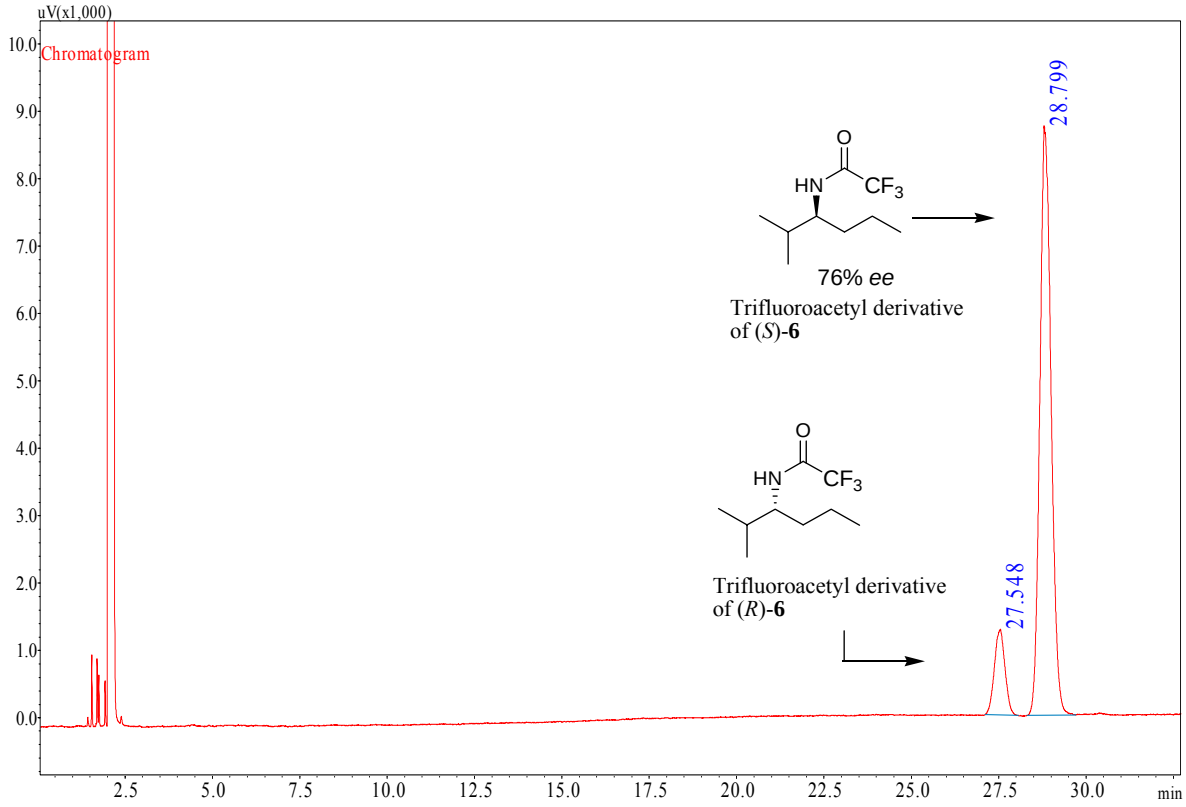

Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 23.062 | 27677.0 | 4613.0 | 9.80292 |
| 2 | 23.290 | 254656.9 | 39811.8 | 90.19708 |




Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 27.956 | 94515.7 | 4498.7 | 50.32334 |
| 2 | 29.348 | 93301.1 | 4228.1 | 49.67666 |




Peak Table-Channel 1

| Peak | Ret. Time | Area | Height | Conc. |
|---|---|---|---|---|
| 1 | 27.548 | 26709.8 | 1268.0 | 12.04077 |
| 2 | 28.799 | 195118.3 | 8741.7 | 87.95923 |